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Efficacy and safety of seven Chinese patent medicines combined with conventional triple/quadruple therapy for *Helicobacter pylori*-positive peptic ulcers: a systematic review and network meta-analysis

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ABSTRACT

Objectives To compare the efficacy and safety of seven Chinese patent medicines (CPMs) combined with conventional triple/quadruple therapy (T/Q) for *Helicobacter pylori*-positive peptic ulcers.

Design A systematic review and network meta-analysis.

Data sources China National Knowledge Infrastructure, VIP database, Wanfang database, ScienceDirect, EBSCO, EMBASE, Web of Science, Cochrane Library and PubMed were searched through 1 June 2022.

Eligibility criteria Randomised controlled trials (RCTs) testing CPMs combined with T/Q for *H. pylori*-positive peptic ulcers were included. The CPMs included Anweiyang capsule, Jianweiyuyang tablets/capsule/granule, Jinghuaweikang capsule, Kangfuxin liquid, Puyuanhewei capsule, Weifuchun tablets/capsule and Weisu granule. At least one of the following outcome indicators was recorded: complete ulcer healing rate (CUHR), effective rate (ER), *H. pylori* eradication rate (*HP*ER), rate of peptic ulcer recurrence (RPUR) and incidence of adverse reactions (IAR).

Data extraction and synthesis Two researchers independently conducted the study selection and extracted data for included studies. The risk of bias was assessed using the Cochrane risk of bias tool. A pairwise meta-analysis was performed using RevMan V.5.3. Network meta-analysis was performed using STATA/MP V.15.0. Confidence in the evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation.

Results A total of 36 RCTs involving 3620 patients were included. Compared with T/Q alone, Weisu+T/Q, Weifuchun+T/Q and Puyuanhewei+T/Q had the highest CUHR, ER and *HP*ER, respectively. Weisu+T/Q and Jianweiyuyang+T/Q had the lowest RPUR and IAR, respectively. The cluster analysis results showed Jianweiyuyang+T/Q might be the best choice concerning efficacy and safety simultaneously, followed by Kangfuxin+T/Q.

Conclusion Among the combination therapies with the CPMs, Jianweiyuyang+T/Q might be the most favourable option for *H. pylori*-positive peptic ulcers, followed by Kangfuxin+T/Q. Considering the limited quantity and quality of the included RCTs, the results should be interpreted with caution.

PROSPERO registration number CRD42022327687.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for network meta-analysis guidelines in the reporting of the study gave credence to the study methodology.
⇒ Taking both efficacy and safety into account, cluster analysis was applied to evaluate the proper rank of the interventions because none of the combination therapies had an absolute advantage over the others.
⇒ The confidence of evidence for the outcomes was assessed using the Grading of Recommendations, Assessment, Development and Evaluation approach.
⇒ The number of randomised controlled trials available in some comparisons was relatively small.

INTRODUCTION

Peptic ulcer disease (PUD) remains a notable health concern, as untreated cases may result in gastroduodenal perforation and bleeding. *Helicobacter pylori* (*HP*) infection is a key risk factor for PUD, disrupting the balance between mucosal defence mechanisms and aggressive factors.[1] The primary treatment for *HP*-positive PUD involves a combination of a proton pump inhibitor (PPI) and two antibiotics (triple therapy), or the addition of bismuth to create quadruple therapy.[2–4] The majority of triple and quadruple therapies demonstrated *HP* eradication rates of up to 70%, with a few regimens achieving rates surpassing 90%.[5]

However, resistance to HP is progressively rising,[6 7] leading to increased complexity in the treatment of *HP* using conventional antibiotics.[8] Studies have indicated a high incidence of adverse reactions (IARs) associated with triple or quadruple therapy, particularly bismuth-containing quadruple therapy.[9 10] Consequently, the consideration of complementary therapeutic approaches is warranted in the management of *HP*-positive PUD.

Traditional Chinese medicine (TCM) has a long history in China, and some TCM materials have strong anti-HP effects,[11 12] can reduce gastric acid secretion and promote mucosa regeneration strongly.[13] Chinese patent medicines (CPMs), which are highly processed forms of TCM, offer advantages such as accessibility, ease of storage, portability and the elimination of the need for decoction. Recent studies have demonstrated the superior efficacy of oral CPMs combined with conventional triple/quadruple therapy (T/Q) in the treatment of *HP*-positive PUD, leading to their endorsement by guidelines[14] and expert consensus.[15 16] However, the comparisons of the various CPMs plus T/Q are still lacking.

Network meta-analysis (NMA), an extension of pairwise meta-analysis (PMA), is a statistical method that compares and ranks different treatments by combining direct and indirect comparisons. In this study, we conducted an NMA to compare and rank the seven CPMs combined with T/Q for treating *HP*-positive PUD to provide a basis for clinical decision-making.

METHODS

The study protocol was registered in PROSPERO (CRD 42022327687) (see online supplemental file 1: CRD42022327687.pdf). This manuscript was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for NMAs checklist[17] (see online supplemental file 2).

Criteria for inclusion and exclusion

Study type

We confined our study design to randomised controlled trials (RCTs) published in Chinese and English. Non-randomised controlled studies, such as observational and laboratory studies, were excluded.

Participants

Patients diagnosed with *HP*-positive PUD were included. PUD was confirmed by gastroscopy. Diagnostic methods for detecting *HP* infection comprised urea breath testing, stool antigen testing, rapid urease testing and histological examination of gastric biopsies obtained during endoscopy. Serological testing for HP antibodies was not employed due to the inability of a positive result to definitively confirm an active infection without age, sex, race or region restriction.[2 3 18]

Interventions

The experimental groups were administered CPMs in combination with T/Q. The CPMs used in the study included Anweiyang capsule (AWY), Jianweiyuyang tablets/capsule/granule (JWYY), Jinghuaweikang capsule (JHWK), Kangfuxin liquid (KFX), Puyuanhewei capsule (PYHW), Weifuchun tablets/capsule (WFC), and Weisu granule (WS). Each CPM was considered as an individual intervention in the analysis.

Controls

The control group received treatment with T/Q. Following the fifth Chinese National Consensus Report on the Management of *HP* Infection[18] and the 2022 Chinese National Clinical Practice Guideline on *HP* Eradication Treatment,[19] quadruple therapy (two antibiotics+PPI+bismuth) is preferred over triple therapy (two antibiotics+PPI) for *HP* infection. However, recent findings from a NMA[20] indicate that not all quadruple therapy regimens are more effective than triple therapy for *HP* eradication. The American College of Gastroenterology Clinical Guideline also[4] suggests that certain triple therapy may be suitable for *HP* eradication. Consequently, both triple therapy and quadruple therapy were considered standard treatment plans in our study. The antibiotic regimen should be limited to a maximum duration of 2 weeks.[2 4 18 19] The triple or quadruple therapy should be identical in the experimental and control groups. Otherwise, the studies would be excluded.

Outcomes measures

At least one of the outcome indicators, such as complete ulcer healing rate (CUHR), effective rate (ER), *HP* eradication rate (*HP*ER), recurrence rate (rate of peptic ulcer recurrence, RPUR) and IAR, must be documented.

Three key points should be highlighted regarding these outcome measures. First, an effective response was characterised by a reduction of more than 50% in the ulcer area following the treatment.[21] Second, successful eradication of *HP* infection was confirmed through urea breath testing, stool antigen testing or rapid urease testing plus histological identification of *HP* (Giemsa staining), at least 4 weeks after discontinuation of medication.[2 4 18] Third, recurrence of peptic ulcer was assessed via gastroscopy 6–12 months post-therapy cessation.

Literature searches

We conducted a comprehensive search of relevant publications up to 1 June 2022 in Chinese-language and English-language databases such as the China National Knowledge Infrastructure, VIP database, Wanfang database, ScienceDirect, EBSCO, EMBASE, Web of Science, Cochrane Library and PubMed. Our search strategy was tailored for each database, using a combination of Mesh, title, abstract, keywords or free-text words. The retrieval terms included Anweiyang, Jianweiyuyang, Jinghuaweikang, Kangfuxin, Puyuanhewei, Weifuchun, Weisu, HP, gastric ulcer, duodenal ulcer and peptic ulcers. The search strategy is available in online supplemental table S1. All the records were concurrently collected and processed in NoteExpress software.

Study selection and data extraction

Two researchers (ZJ and BD) independently selected studies based on predefined inclusion and exclusion criteria. Data were extracted using a preset data extraction form by BD and YQ Zhang. The information extracted encompassed vital publication details (name of the first author, year of publication), participant characteristics (sample size, age, sex, disease duration and ulcerated area or diameter), intervention specifics and outcome indicator data. Disagreements were resolved through discussions with a third researcher (ZY or YC).

Quality of bias assessment of included studies

The quality of the included studies was assessed according to the Cochrane risk of bias tool,[22] including the adequate method for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Two researchers (ZJ and YL) independently assessed the risk of bias, and any disagreement was resolved by discussion with a third researcher (ZY or YC).

Data analysis

Pairwise meta-analysis

PMA was conducted using RevMan V.5.3 software. Relative risk (RR) with a 95% CI was calculated for the dichotomous outcomes. Heterogeneity among the included studies was evaluated using the I^2 statistic. Substantial heterogeneity, defined as I^2 statistics exceeding 50%, prompted the utilisation of the random-effects model for PMA, while the fixed-effects model was employed in other instances.

Network meta-analysis

The NMA was conducted using the network package in STATA/MP V.15.0, wherein the RR with a 95% CI for the dichotomous outcomes was calculated. Statistical significance was set at $p<0.05$. The surface under the cumulative ranking (SUCRA) was calculated to rank each treatment.[23] The cluster analysis was used to evaluate the effectiveness and safety of the interventions and determine the optimal CPMs. Additionally, the summary results of all pairwise comparisons and NMAs were presented in the league tables.

Network plots were constructed to visualise the comparisons. Each node represented an intervention, and its size was weighted by the number of subjects in each intervention. The thickness of the connecting line represented the number of included studies.[23] If there were closed loops in the intervention structure, the inconsistency of the evidence should be assessed.[24]

The 95% predictive interval (95% PI) was calculated to describe the heterogeneity in this NMA. Uncertainty stemming from heterogeneity was characterised by discrepancies between the 95% CIs and their corresponding 95% PI.[23 25] In instances of substantial heterogeneity, sensitivity analyses were performed by excluding potentially biased studies. Transitivity was examined by assessing the distributions of potential effect modifiers across comparisons. These effect modifiers encompassed the following items: age, disease duration, ulcerated area or diameter, duration of the antibiotic course, duration of the full therapeutic course and the case numbers of duodenal ulcer, gastric ulcer and compound ulcer. Additionally, publication bias was assessed using a funnel plot where a symmetrical funnel suggests little bias.

Certainty of the evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to assess the confidence of evidence for the outcomes of the NMA.[26–28] The certainty of the NMA estimates was rated as 'high', 'moderate', 'low' or 'very low' based on considerations of risk of bias, inconsistency, indirectness, imprecision and publication bias.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Selection and identification of studies

The literature search yielded a total of 2452 studies. As indicated in figure 1, the full text of 393 references was screened after title and abstract screening. Ultimately, 36 two-armed RCTs[29–64] met the eligibility criteria and were included in the NMA. All studies were performed in China, and the publication years ranged from 2008 to 2022.

Characteristics of included studies

36 RCTs[29–64] involving 3620 patients were included. 1830 patients received combination therapy (CPM+T/Q), and 1790 patients received T/Q alone. The duration of the full therapeutic course ranged from 2 to 8 weeks. Among the included studies, AWY, JHWK, JWYY, KFX, PYHW, WFC and WS were studied in 1, 10, 2, 16, 2, 2 and 3 trials, respectively. The characteristics of the 36 eligible RCTs are presented in online supplemental table S2. The characterisations of the seven CPMs are presented in online supplemental table S3. The summary of the outcomes data in the 35 included studies is presented in online supplemental table S4.

Risk of bias of included studies

All of the included studies mentioned randomisation, with only 12 trials[31 38 39 50 52 54–57 59 61 63] providing detailed descriptions of their randomisation methods, which were categorised as 'low risk'. The majority of RCTs were deemed to have an 'unclear risk' in terms of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting and other biases, due to inadequate information. However, two studies were found to have a high risk of bias related

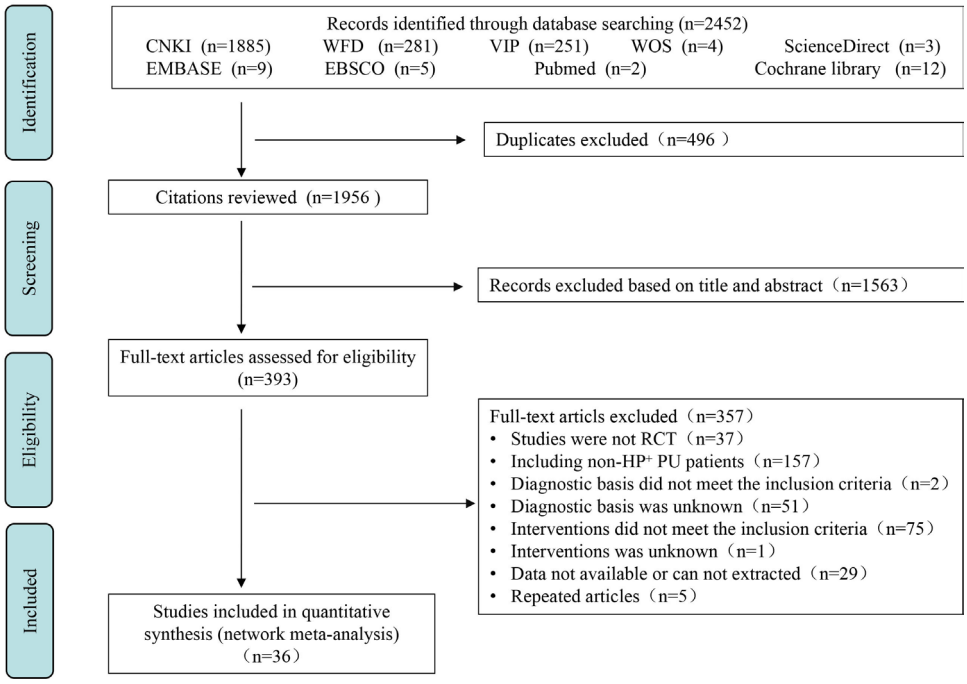

Figure 1 A flow diagram of the literature screening and selection processes. CNKI, China National Knowledge Infrastructure; HP, *Helicobacter pylori*; PU, peptic ulcer; RCT, randomised controlled trial; WFD, Wanfang database; WOS, Web of Science.

to blinding[29 63] as the duration of the full therapeutic course differed between the control and experimental groups, potentially leading to variation in the IARs. All outcomes were laboratory measurements in nineteen RCTs[30 32–35 37 40 42 43 47 49–53 58 60 61 64] and unlikely to be influenced by lack of blinding, indicating a low risk of bias for blinding in these studies. Additionally, the risk of bias for incomplete outcome data was low in 33 studies, with only 3 RCTs[49 55 59] classified as 'high risk' due to a high number of patients lost to follow-up. In terms of selective reporting, one RCT[48] was considered to have a 'low risk' as all five outcomes were reported. The risks of biases in the included studies are presented in online supplemental figure S1 and online supplemental figure S2. Overall, most studies demonstrated a moderate risk of bias in the seven domains assessed.

Results of the PMA

We assessed the impact of CPMs on CUHR, ER, *HP*ER, RPUR and IAR. Compared with T/Q alone, AWY+T/Q (RR 1.55, 95% CI 1.04 to 2.30), JHWK+T/Q (RR 1.19, 95% CI 1.09 to 1.31), JWYY+T/Q (RR 1.39, 95% CI 1.07 to 1.82), KFX+T/Q (RR 1.30, 95% CI 1.22 to 1.39), PYHW+T/Q (RR 1.81, 95% CI 1.19 to 2.77), WFC+T/Q (RR 1.18, 95% CI 1.06 to 1.32) and WS+T/Q (RR 2.08, 95% CI 1.18 to 3.67) displayed significantly improved CUHR; KFX+T/Q (RR 1.10, 95% CI 1.07 to 1.14) and WFC+T/Q (RR 1.12, 95% CI 1.05 to 1.20) displayed significantly improved ER; JHWK+T/Q (RR 1.14, 95% CI 1.08 to 1.21), JWYY+T/Q (RR 1.31, 95% CI 1.01 to 1.70), KFX+T/Q (RR 1.13, 95% CI 1.03 to 1.23) and PYHW+T/Q (RR 1.46, 95% CI 1.04 to 2.04) displayed significantly improved *HP*ER; KFX+T/Q (RR 0.39, 95% CI 0.28 to 0.53) and WS+T/Q (RR 0.26, 95% CI 0.10, 0.67) significantly reduced RPUR (see online supplemental table S5 and online supplemental table S6). No significant difference was observed in any comparisons among the interventions in terms of IAR (see online supplemental table S5 and online supplemental table S7).

In terms of ER, the results of the heterogeneity test indicated significant heterogeneity among the different interventions with I^2 values of 96% for JHWK+T/Q versus T/Q, I^2 values of 57% for WS+T/Q versus T/Q, necessitating the use of random-effects models. The other comparisons with I^2<50% did not exhibit significant heterogeneity, necessitating the use of fixed-effects models (see online supplemental table S5).

Results of the NMA

Evidence network

The network plots are presented in figure 2. All the combined therapies of CPM plus T/Q had at least one comparison with T/Q alone while all of the combined therapies lacked a closed loop between them, indicating that inconsistency testing was unnecessary.

Complete ulcer healing rate

28 RCTs[29 33–52 55–57 59–61 63] with 8 interventions reported CUHR. AWY+T/Q (RR 1.55, 95% CI 1.01 to 2.37), JHWK+T/Q (RR 1.16, 95% CI 1.03 to 1.30), JWYY+T/Q (RR 1.39, 95% CI 1.06 to 1.83), KFX+T/Q (RR 1.26, 95% CI 1.17 to 1.36), PYHW+T/Q (RR 1.81, 95% CI 1.16 to 2.84) and WS+T/Q (RR 2.08, 95% CI 1.16 to 3.74) displayed significantly improved CUHR compared with T/Q alone. However, no significant difference was observed in any comparisons among

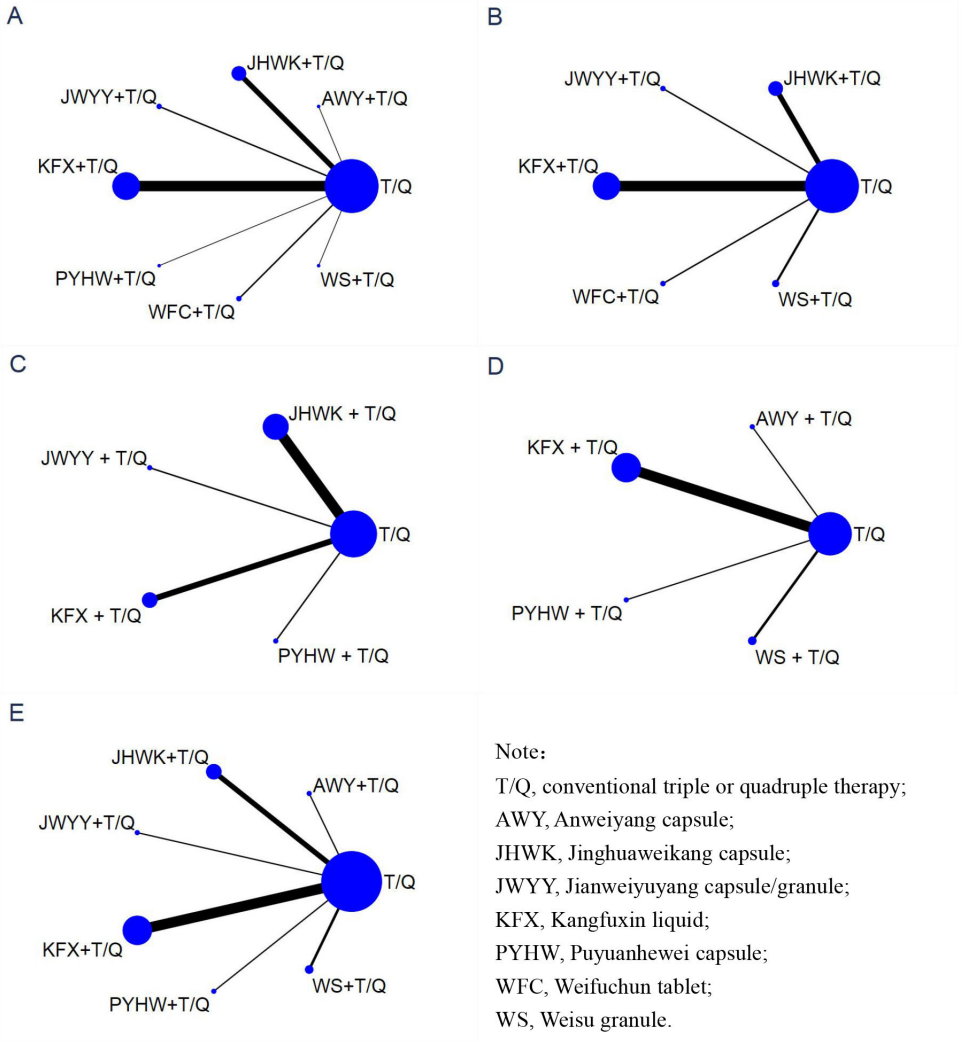

Figure 2 Network plots of the outcomes. (A) complete ulcer healing rate; (B) effective rate; (C) *HP* eradication rate; (D) rate of peptic ulcer recurrence; (E) incidence of adverse reactions. HP, *Helicobacter pylori*.

the combined therapies (see figure 3A and online supplemental table S6). According to the SUCRA values, WS+T/Q ranked first for improving CUHR, followed by PYHW+T/Q and AWY+T/Q (see online supplemental table S8).

Effective rate

28 RCTs[32–36 38–48 50 51 53–57 60–64] with 6 interventions reported ER. JHWK+T/Q (RR 1.10, 95% CI 1.02 to 1.17), KFX+T/Q (RR 1.09, 95% CI 1.04 to 1.14) and WFC+T/Q (RR 1.13, 95% CI 1.02 to 1.25) displayed significantly improved ER compared with T/Q alone. No other comparisons revealed significant differences (see figure 3B and online supplemental table S6). According to the SUCRA values, WFC+T/Q ranked first for improving ER, followed by WS+T/Q, JHWK+T/Q and JWYY+T/Q (see online supplemental table S8).

HP eradication rate

13 RCTs[30–32 35–38 40 48 51 52 57 58] with 5 interventions reported *HP*ER. JHWK+T/Q (RR 1.12, 95% CI 1.06 to 1.18), JWYY+T/Q (RR 1.31, 95% CI 1.01 to 1.70), KFX+T/Q (RR 1.12, 95% CI 1.03 to 1.23) and PYHW+T/Q (RR 1.46, 95% CI 1.04 to 2.04) displayed significantly improved *HP*ER compared with T/Q alone. However, no significant difference was observed in any comparisons among the combined therapies (see figure 3C and online supplemental table S6). According to the SUCRA values, PYHW+T/Q ranked first for improving *HP*ER, followed by JWYY+T/Q and KFX+T/Q (see online supplemental table S8).

Rate of peptic ulcer recurrence

12 RCTs[29 43 44 47 48 51 52 55 56 59 63 64] with 5 interventions reported RPUR. KFX+T/Q (RR 0.40, 95% CI 0.29 to 0.56) and WS+T/Q (RR 0.27, 95% CI 0.10 to 0.69) significantly reduced RPUR compared with T/Q alone. No other comparisons revealed significant differences (see figure 3D and online supplemental table S6). According to the SUCRA values, WS+T/Q ranked first for reducing RPUR, followed by AWY+T/Q and KFX+T/Q (see online supplemental table S8).

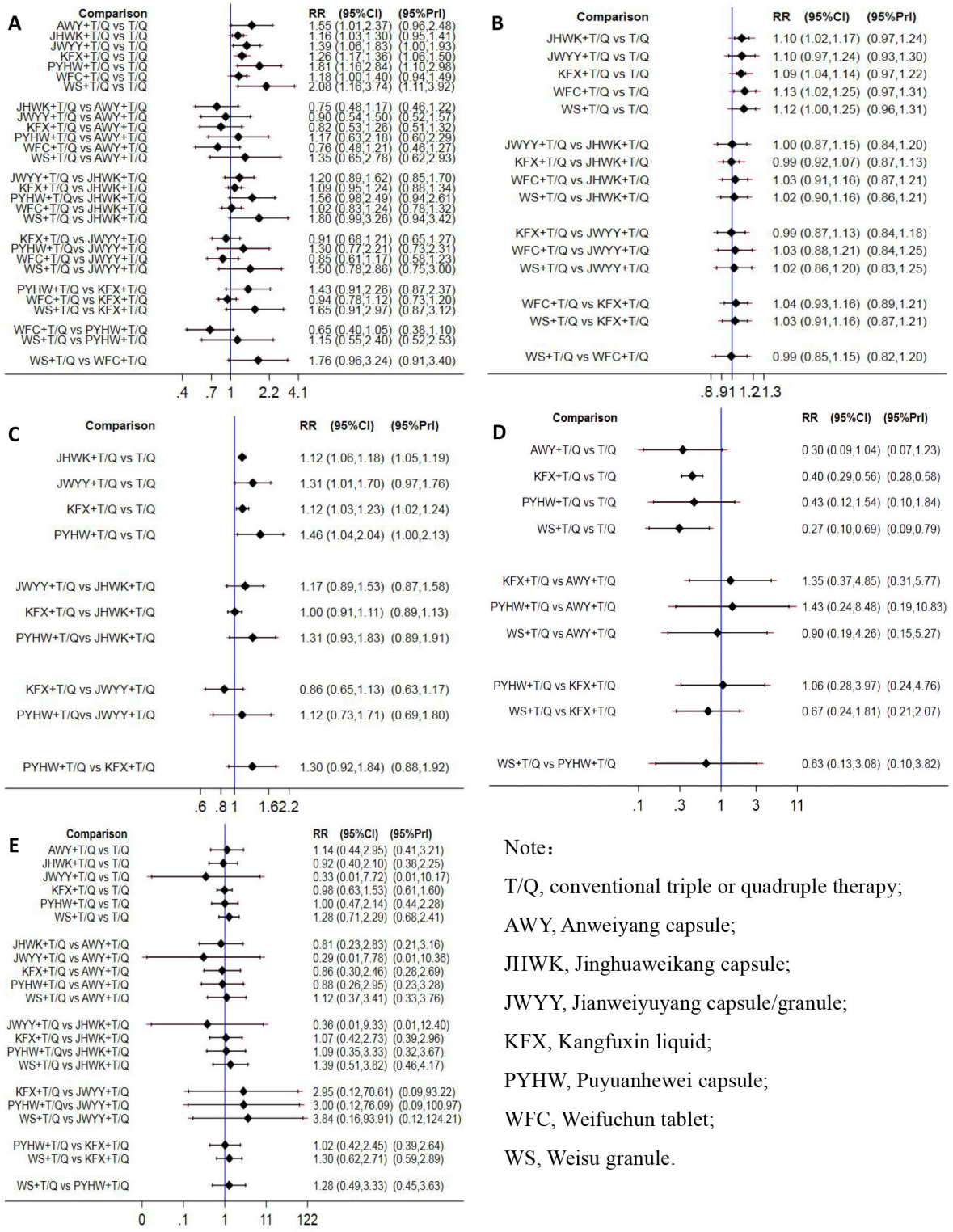

Figure 3 Predictive interval plots of the outcomes. (A) Complete ulcer healing rate; (B) effective rate; (C) *HP* eradication rate; (D) rate of peptic ulcer recurrence; (E) incidence of adverse reactions. HP, *Helicobacter pylori;* RR, relative risk.

Incidence of adverse reactions

17 RCTs[29 31 36 38 39 41 44–46 48 54–57 59 62 63] with 7 interventions reported IAR. No significant difference was observed in any comparisons among the interventions (see figure 3E and online supplemental table S7). According to the SUCRA values, JWYY+T/Q ranked first for reducing IAR, followed by JHWK+T/Q and KFX+T/Q (see online supplemental table S8).

Cluster analysis

Cluster ranking considering both efficacy and safety was performed to simultaneously weigh the risks and

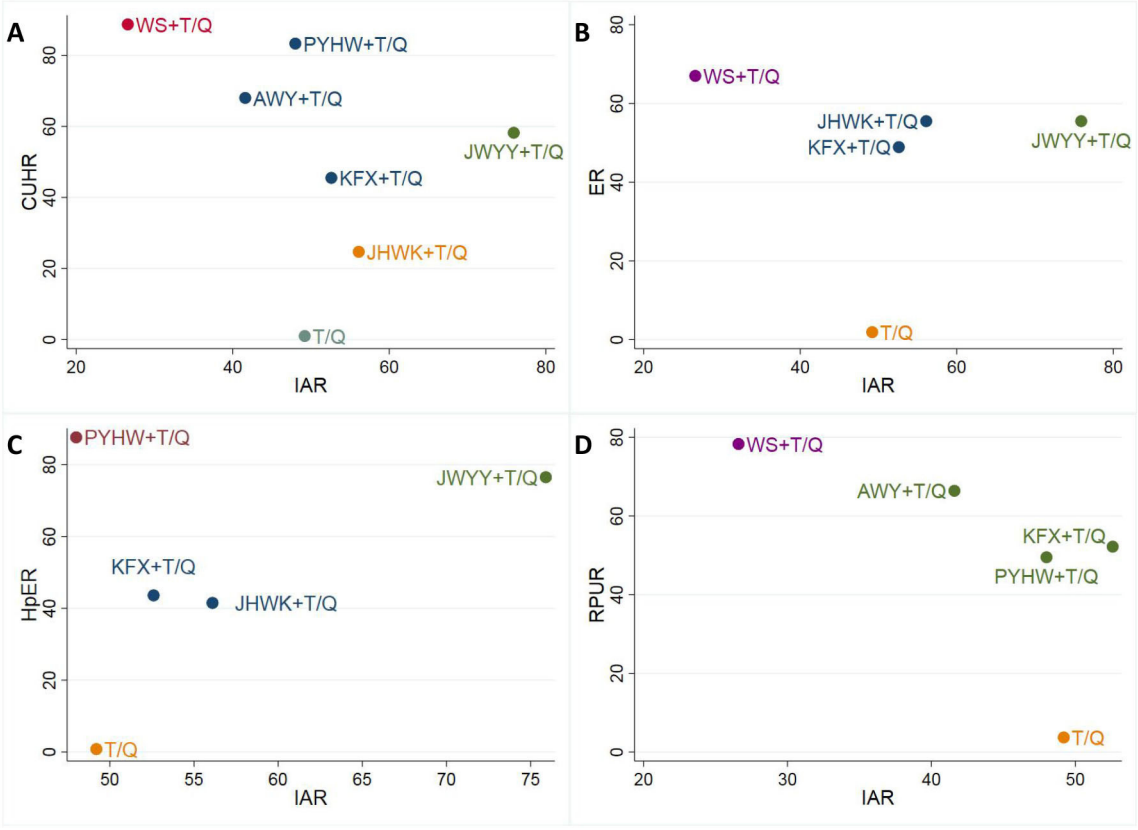

Figure 4 Cluster analysis plots. (A) IAR (x-axis) and CUHR (y-axis); (B) IAR (x-axis) and ER (y-axis); (C) IAR (x-axis) and *HP*ER (y-axis); (D) IAR (x-axis) and RPUR (y-axis). AWY, Anweiyang capsule; CUHR, complete ulcer healing rate; ER, effective rate; *HP*ER, *Helicobacter pylori* eradication rate; IAR, incidence of adverse reactions; JHWK, Jinghuaweikang capsule; JWYY, Jianweiyuyang capsule/granule; KFX, Kangfuxin liquid; PYHW, Puyuanhewei capsule; RPUR, rate of peptic ulcer recurrence; T/Q, conventional triple or quadruple therapy; WFC, Weifuchun tablet; WS, Weisu granule.

benefits of each intervention. Each cluster was assigned a specific colour, with interventions located in the upper right corner deemed superior. The results of the cluster analysis, based on SUCRA values for IAR and CUHR (see figure 4A), indicated that JWYY+T/Q was the most effective and safe intervention, followed by a cluster containing KFX+T/Q. This trend was also observed in the cluster analysis based on SUCRA values for IAR and ER (see figure 4B), as well as SUCRA values for IAR and *HP*ER (see figure 4C). KFX+T/Q was one of the best treatment strategies based on the cluster analysis results using SUCRA values for IAR and RPUR (see figure 4D). In contrast, T/Q alone might be the worst treatment strategy considering the comprehensive rank of cluster analysis.

Heterogeneity check

The heterogeneity test revealed that none of the comparisons involving RPUR and IAR was affected by the estimated heterogeneity, as indicated by consistent 95% CIs and respective 95% PIs (see figure 3D,E), ensuring the stability of the estimations of NMA. Three of the 28 comparisons involving CUHR (see figure 3A), 3 of the 15 comparisons involving ER (see figure 3B) and 2 of the 10 comparisons involving *HP*ER (see figure 3C) were influenced by estimated heterogeneity because their 95% CIs and respective 95% PIs were inconsistent. The estimate of heterogeneity tau^2 for the NMA of CUHR, ER and *HP*ER was 0.01, 0 and 0, respectively, suggesting low levels of heterogeneity and relatively stable estimations in the NMA.

Funnel plot and publication bias

The funnel plots are shown in online supplemental figure S3. Scatters in the funnel plot for CUHR, *HP*ER, RPUR and IAR were almost visually symmetrical, suggesting low publication biases. However, the funnel plots for ER displayed a slightly asymmetrical distribution, hinting at the possibility of publication bias.

Certainty of the evidence

Online supplemental table S9 provides a summary of the certainty of evidence for the outcomes. The certainty of evidence was very low for all the comparisons among the combined therapies, due to study limitations (most information is from studies at unclear risk of bias, downgrade one level), indirectness and imprecision. The certainty of evidence was low for most of the direct comparisons between CPMs+T/Q and T/Q because of study limitations, inconsistency (due to heterogeneity) and imprecision. Regarding CUHR, *HP*ER and RPUR, there was moderate confidence in estimates supporting the use of

CPMs+T/Q over T/Q alone. For example, the CPMs were JWYY, KFX and WS with respect to CUHR.

DISCUSSION

PUD is a prevalent gastrointestinal disorder that poses a significant risk to human health.[65] TCMs, including CPMs, have been frequently used for the treatment of PUD. The PMA and NMA were conducted to evaluate the efficacy and safety of the seven CPMs in combination with T/Q for the management of PUD. The results indicated that seven combination therapies (CPMs+T/Q) were notably more effective in improving CUHR, ER, *HP*ER or reducing RPUR compared with T/Q alone across at least one outcome measure. Furthermore, the ranking results demonstrated that T/Q alone consistently ranked lowest in the aforementioned indicators, highlighting the superior efficacy of the combined treatment approach. As for IAR, no significant difference was observed among the interventions. Consequently, the integration of CPMs in combination therapies could enhance efficacy while maintaining safety.

Based on the results of this study, each combination therapy involving CPMs had its advantages and disadvantages. WS+T/Q ranked first, second and first in improving CUHR, ER and reducing RPUR, respectively, might exhibit superior efficacy. However, WS+T/Q ranked last with the highest IAR among the interventions, indicating a potential safety concern. AWY+T/Q and PYHW+T/Q showed less favourable safety profiles because they ranked fifth and sixth. The efficacy of WFC+T/Q and JHWK+T/Q was less than satisfactory due to their ranks in improving CUHR. Overall, none of the combination therapies were deemed completely satisfactory. Cluster analysis was used to further assess the rankings of the interventions. JWYY+T/Q was the best treatment strategy among the interventions considering the safety (IAR) and efficacy (CUHR, ER and *HP*ER), followed by a cluster including KFX+T/Q. Simultaneously, the optimal bunch with lower RPUR and IAR also encompassed KFX+T/Q. Therefore, JWYY+T/Q might be deemed the most advantageous choice, followed by KFX+T/Q. An NMA[66] of Chinese herbal formulae for *HP*-positive PUD showed that the combination therapies involving TCMs held clinical significance. These Chinese herbal formulas included three CPMs such as JHWK, KFX and WFC. The results of this NMA showed that combination therapy with KFX could be the superior option among these combination therapies with CPMs, aligning with the results of our study.

Several studies have been undertaken to investigate the underlying mechanisms for CPMs against PUD. It is known that JWYY has inhibitory effects on gastric acid secretion and pepsin activity[67] and could improve gastrointestinal mucosa surface hydrophobicity and mucous gel layer stability,[68–70] thereby inhibiting mucosal damage. In addition, JWYY could stimulate angiogenesis and promote mucosal regeneration by increasing platelet-derived growth factor and transforming growth factor.[71 72] KFX can inhibit inflammation and oxidative stress by reducing the expression of inflammatory factors and thus inhibit mucosal damage.[73–75] KFX could also stimulate angiogenesis, promote mucosal regeneration and enhance growth factor expression.[73–75] Taken together, JWYY and KFX demonstrated strong efficacy in preventing mucosal injury, enhancing defence mechanisms in the gastrointestinal mucosa and promoting mucosal repair. These studies and findings provided strong evidence to support our research.

Numerous combination therapies with CPMs have been reported to be available for treating PUD patients with *HP*. However, there is a lack of direct evidence comparing these combined therapies. As the first NMA to compare seven combination therapies with CPMs and T/Q, our study provided valuable insight for selecting the appropriate treatment option. Nevertheless, some limitations need to be improved. First, the quality of the included studies was unsatisfactory. Although all the studies included were RCTs, 24 of them failed to appropriately describe the methods of random allocation. Additionally, none of the included studies mentioned allocation concealment or blinding methods. IAR might, therefore, be affected in the RCTs. Second, the rapid urease test or the test performed within a timeframe of less than 4 weeks postcessation of medication may yield false-negative outcomes, rendering it unsuitable for evaluating *HP* eradication.[2 3] The data pertaining to *HP*ER from certain RCTs[29 39 41–44 46 47 54 55 59–61 63] were excluded, influencing the overall analysis due to the relative sample size. Consequently, it is advisable to carefully choose an appropriate detection method to ascertain the recurrence of PUD.[2 4 18] Third, the RPUR was reported in only 12 of the 36 included RCTs, potentially impacting the accuracy of our findings. Fourth, it was known that factors such as patients' age, current smoking and/or drinking habits, the locations and sizes of ulcers, antibiotic resistance of *HP*, various T/Q therapy regimens and recent use of non-steroidal anti-inflammatory drugs (NSAIDs) could be identified as the effect modifiers.[76–78] Baseline comparisons between arms revealed no significant differences in patients' ages or the locations and sizes of ulcers (see online supplemental table S2). However, variations in antibiotic regimens and the duration of therapeutic courses could potentially introduce heterogeneity. Furthermore, current smoking and/or drinking habits, antibiotic resistance of *HP* and recent use of NSAIDs were not addressed in the included studies. In light of potential heterogeneity, heterogeneity tests were performed for each outcome in this NMA. It is known that the prediction interval can tell us how much the effect size varies and can be used to evaluate the impact of effect measure modification.[79] In the absence of between-study heterogeneity, the prediction interval coincides with the respective CI.[25] Within this NMA, the heterogeneity test results showed that only 8 of 84 comparisons involving 5 outcomes, including

3 of the 28 comparisons involving CUHR, 3 of the 15 comparisons involving ER and 2 of the 10 comparisons involving *HP*ER, were influenced by estimated heterogeneity, while the comparisons involving RPUR and IAR were not influenced by estimated heterogeneity. Therefore, we contended that most of the results of the comparisons among the interventions in this NMA were stable and reliable, as evidenced by the prediction interval data. It should be noted, however, that the precision of the prediction interval may be compromised by the limited number of studies included.

The seven combination therapies with CPMs have been extensively used in clinical settings due to their safety and proven efficacy. Moving forward, more high-quality RCTs would be included to improve the reliability and stability of NMA by providing more robust outcome indicators.

Conclusions

JWYY+T/Q might be the most favourable option for *HP*-positive PUD among the seven combination therapies with the CPMs, followed by KFX+T/Q. However, this finding should be interpreted with caution due to the limited available evidence. Further high-quality RCTs are necessary to assess the effectiveness and safety of these CPMs in managing *HP*-positive PUD.

Contributors ZJ conceived the study, drafted the protocol, screened citations and full-text articles, assessed the quality of the included studies, performed the statistical analysis, wrote the manuscript and is the manuscript guarantor. BD screened citations and full-text articles and participated in data extraction. YZ participated in data extraction. YL assessed the quality of the included studies. ZY resolved discrepancies in the process of literature screening and data extraction. HD conceived the study and drafted the protocol. YC conceived the study and resolved discrepancies in the process of literature screening and data extraction. All authors reviewed and revised the manuscript, approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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